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The Emergence of Single Neurons in Clinical Neurology

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Single neuron actions and interactions are the sine qua non of brain function, and nearly all diseases and injuries of the CNS trace their clinical sequelae to neuronal dysfunction or failure. Remarkably, discussion of neuronal activity is largely absent in clinical neuroscience. Advances in neurotechnology and computational capabilities, accompanied by shifts in theoretical frameworks, have led to renewed interest in the information represented by single neurons. Using direct interfaces with the nervous system, millisecond-scale information will soon be extracted from single neurons in clinical environments, supporting personalized treatment of neurologic and psychiatric disease. In this Perspective, we focus on single-neuronal activity in restoring communication and motor control in patients suffering from devastating neurological injuries. We also explore the single neuron's role in epilepsy and movement disorders, surgical anesthesia, and in cognitive processes disrupted in neurodegenerative and neuropsychiatric disease. Finally, we speculate on how technological advances will revolutionize neurotherapeutics.

Introduction

Readers of this journal will hopefully forgive us for feeling the need to state what is obvious to any student of neuroscience—the activity of single neurons, the action potential in particular, is a central component of normal brain function. Yet this bedrock fact has remarkably little outward presence in the daily practice of clinical neurology, neurosurgery, or psychiatry. The only references to single-neuron activity and action potentials in searching through classic textbooks of neurology (e.g., Adams and Victor's 8th edition, Ropper and Brown, eds. [Ropper et al., 2005]) are related to peripheral nerves. We would also hazard that the majority of practicing neurologists and neurology resident physicians would be hard pressed to explain the underlying physiology of the action potential in anything beyond a saltatory fashion. Most would also find it difficult to discuss how any greater understanding would play into diagnostic or therapeutic decisions for their patients.

This state of affairs is not surprising for many reasons. Arguably, much of the pathology that is seen in routine clinical practice, such as stroke, trauma, inflammation, infection, and tumors, are not recognized or considered to be diseases of the individual neuron. Even motor neuron disease, demyelinating diseases, and other neurodegenerative diseases are not, in toto, diseases of an individual neuron; they are manifestations of a more widespread pathology. Perhaps even more important to the general clinical neglect of the single neuron is the previous absence of relevant technology. Until recently there were essentially no diagnostic examinations or therapeutic interventions that could target modest groups of neurons let alone single neurons. While the spatial resolution of modern structural and fMRI, the temporal sensitivity of electroencephalography (EEG) or magnetoencephalography (MEG), and the exploding capabilities of genetics and proteomics are remarkable, they are not capable of resolving neuronal activity at its most fundamental scale of the action potential and its firing rates or patterns (Figure 1). Also until recently, only in animal models have the physiologic activities of small populations of individual neurons been examined, and this by only a relatively small subset of laboratories.

Emergence of New Technologies for Studying Single-Unit Activity in the Human Brain

Over the past dozen years, technological advances have supported substantial progress in the understanding of common neurological problems, and novel therapeutic and restorative approaches now incorporate the role of individual neurons and action potentials. Many factors have contributed to these breakthroughs. Improved surgical techniques, advances in computer processing speed, size, efficiency, and affordability, and increased interaction among divergent fields (i.e., electrical engineering, computer science, neuroscience, neurology, neurosurgery, etc.) have all enabled increased, clinically indicated single-unit recordings in human cortex. The primary technological advance has been the deployment of multi-neuronal recording modalities suitable for use in humans and the related development of research protocols and clinical trials employing such neurotechnologies.

Single-unit recordings in humans have been performed since the mid-1950s (Ward and Thomas, 1955; Rayport and Waller, 1967; Marg and Adams, 1967; Rayport et al., 1969). While human single-unit recordings from subcortical or cortical structures were sporadic through the turn of the century (see Figure 2), they were instrumental in deepening our understanding of basal ganglia function and Parkinson's disease, neocortical function and epilepsy. In 1971, Verzeano, Crandall, and Dymond (with

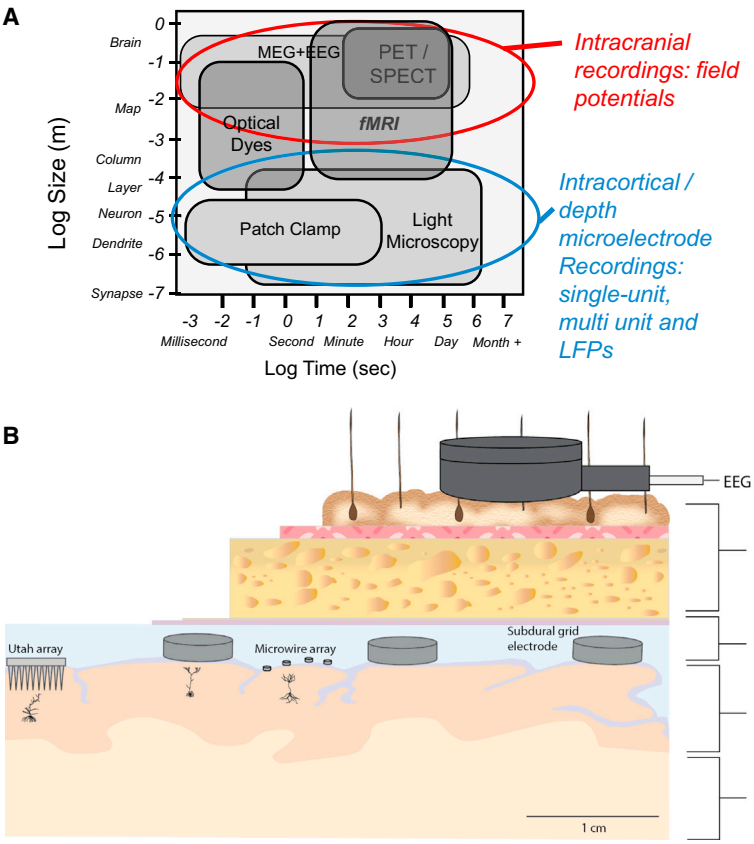

Figure 1. Multiple Spatio-Temporal Scales of Recording Resolution in the Nervous System

(A) Spatio-temporal resolution of different recording systems with implications for relative advantages and disadvantages (adapted from Churchland and Sejnowski, 1988). Current and emerging technologies now allow for single-unit resolution in the context of larger-scale recordings that can provide millisecond resolutions for days, weeks, months, or years.

(B) A schematic of the spatial relationships between different forms of human extra- and intracranial recordings and the areas they cover as well as their specificity for individual neurons.

technical assistance from Everett Carr and Sam Brakel; E. Halgren, personal communication) reported on the use of fine wires inserted through the center of a depth electrode to record single-unit activity chronically in the amygdala of a patient with epilepsy (Verzeano et al., 1971). Over the next two decades, this approach was used to explore neuronal signaling during epileptiform activity, in response to changes in metabolic state or level of arousal, and during normal cognition (Halgren et al., 1977a, 1977b, 1977c, 1978; Ravagnati et al., 1979; Babb et al., 1981; Wilson et al., 1983). The same approach was later refined and augmented by Fried and Benhke in what has now become a standard approach to obtain multiple single-unit recordings from deep brain structures in humans (Fried et al., 1999). At about the same time, Richard Norman created an etched silicon array of 100 probes, known as the Utah array, which has been used extensively in rodent, feline, and nonhuman primate experiments and also in human neocortical research (discussed below). Together, there are now at least four high-resolution neuronal recording platforms that can be used in acute, subacute, and even chronic settings. Each delivers some level of single-neuron activity to the researcher. These include microwire bundles as discussed above, an array of microelectrodes arranged in laminar fashion (Ulbert et al., 2001), microelectrode contacts arranged on a grid for use above the pia or on the shaft of a depth electrode (Worrell et al., 2008), and the 96 contact Utah array (currently available through BlackRock microsystems as the NeuroPort array; [Nordhausen et al., 1994, 1996; Maynard et al., 1997]). These systems (Figure 3) augment with chronic recording capabilities the more classical microprobe used in the placement of depth electrodes for the relief of symptoms of Parkinson's disease. In addition, there are now multiple vendors selling high-channel count, high-sampling rate recording systems that are intended for use in clinical research contexts. Electronics are becoming even further miniaturized and new materials and wireless, fully implanted methods are becoming available (for example, see Borton et al., 2013; Yin et al., 2014; Khodagholy et al., 2015); note that there are many important research endeavors in this field which are beyond the scope of this Perspective.

Accompanying this dramatic increase in the ability to record single neurons have been several related computational neuroscience advances. First among these are new methods for extracting spiking information from large datasets. These "clustering" algorithms are now available in a variety of different forms with optimization for high speed (essentially real time) and for working with particularly large datasets. Parallel computer science advances permit low-cost and relatively efficient storage and transfer of neural datasets that approach and sometimes exceed the Tb range. The increasing use of high-bandwidth recordings in the clinical setting is yielding huge and complex datasets that are stretching our abilities to process those data efficiently or meaningfully. This is particularly true when trying to efficiently capture and display both spatial and temporal patterns of large-scale neuronal activity. New developments in data reduction techniques (e.g., Mante et al., 2013; Vargas-Irwin et al., 2015) are early indicators that novel approaches are becoming available for dealing with this challenging and exciting opportunity to gain a deeper understanding, and correspondingly increasing clinical utility, of the neuronal ensemble activity underlying both normal and pathological function.

Single-Cortical Neurons and Restoring Motor Function

A longstanding goal of neuroscience research has been to understand the neural basis for voluntary action, with an ultimate

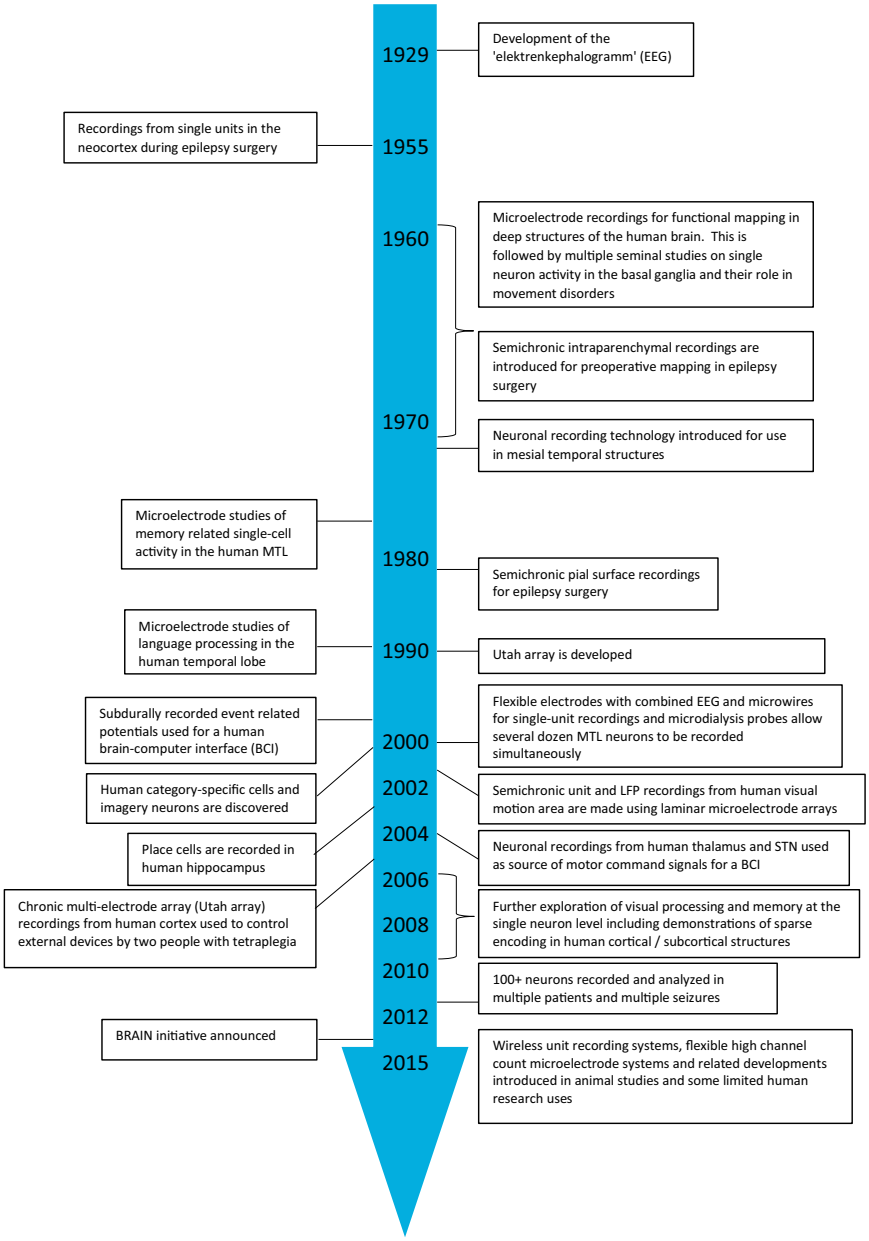

Figure 2. Timeline of Major Advances in Single-Unit Neuronal Analysis in Human Cortex and Subcortical Structures

objective of restoring mobility to people affected by a wide variety of neurological disorders causing paralysis (Frank, 1968; Humphrey et al., 1970, 1997; Pancrazio and Peckham, 2009; Pancrazio, 2009). Brain-computer interface (BCI) technology is based on directly linking neural activity to either an external device or to internal effectors including the spinal cord, peripheral nerves, or muscles. Such an approach is designed to improve the independence of individuals with severe physical disability by offering a robust and intuitive method of interfacing with assistive devices.

Initial research was focused on understanding the neural encoding of movement. Largely through research with nonhuman primates, a foundation was developed for understanding the anatomic and functional organization of primary motor cortex and other motor-related areas (Evarts, 1966, 1967, 1968a, 1968b; Fetz, 1969; DeLong, 1971; DeLong and Strick, 1974; Tanji and Evarts, 1976; Weinrich and Wise, 1982; Georgopoulos et al., 1982, 1984, 1989; Wise, 1985, 1993; Donoghue, 1985; DeLong et al., 1986; Kettner et al., 1988; Schwartz et al., 1988; Caminiti et al., 1990; Sanes et al., 1990; Kalaska and Crammond, 1992; Ashe and Georgopoulos, 1994; Donoghue and Sanes, 1994; Fu et al., 1995; Taira et al., 1996; Scott and Kalaska, 1997; Shen and Alexander, 1997; Hatsopoulos et al., 1998; Wise et al., 1998; Sergio and Kalaska, 1998; Kakei et al., 1999; Moran and Schwartz, 1999; Gandolfo et al., 2000; Sanes and Donoghue, 2000; Ajemian et al., 2000; Li et al., 2001; Todorov and Jordan, 2002; Paz et al., 2003; Kemere et al., 2004; Paninski et al., 2004a, 2004b; Paz and Vaadia, 2004; Churchland et al., 2006; Wu and Hatsopoulos, 2006; Churchland and Shenoy, 2007; Graziano, 2011; Oby et al., 2013; Barrese et al., 2013). This research demonstrated that information about many aspects of movement could be extracted from the activities of individual neurons. As part of the NIH Neural Prosthesis Program (Pancrazio, 2009), research beginning in the mid-1990s demonstrated that simple movements could be decoded in real time from the spiking activities of multiple neurons in motor cortex in nonhuman primates and that nonhuman primates could use these spiking patterns to control a computer cursor in two or three dimensions to control robotic limbs (Humphrey and Hochberg, 1995; Burrow et al., 1997; Chapin et al., 1999; Fetz, 1999; Taylor et al., 2002; Serruya et al., 2002; Nicolelis et al., 2003; Carmena et al., 2003; Musallam et al., 2004; Santhanam et al., 2006; Velliste et al., 2008; Jarosiewicz et al., 2008).

Until recently, however, these studies occurred solely in nonhuman primate research labs and the results had not yet reached the realm of discussion among clinicians. A first effort to translate prior single-unit nonhuman primate neurophysiology research toward clinical populations used a proprietary "cone" or "neurotrophic" electrode which was placed in a few people with advanced ALS or brainstem stroke (Kennedy et al., 1992a, 1992b, 2000; Kennedy, 1989; Kennedy and Bakay, 1998).

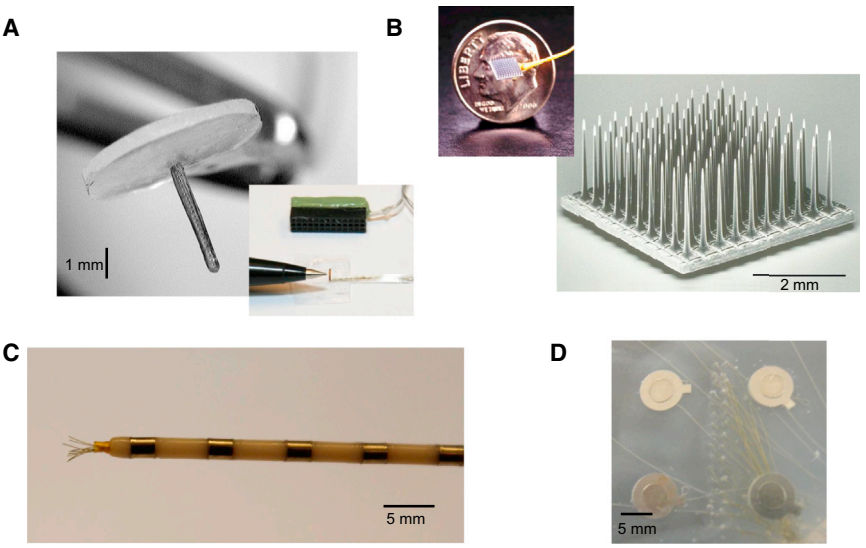

Figure 3. Multielectrode Recording Systems for Microscale Neurophysiology in Humans
(A) Laminar microelectrode array.
(B) "Utah" microelectrode array.
(C) Microwire array for use in depth electrodes used to reach mesial temporal structures.
(D) Microgrid of fine wires (center) between macroelectrode contacts on a silastic sheet used to record at high-spatial resolution from the pial surface.

A breakthrough in translating preclinical animal studies to clinical research resulted from the formation of a company launched out of John Donoghue's laboratory at Brown University in 2002, Cyberkinetics, which manufactured and commercialized the Utah array and associated recording equipment and readied a complete Neural Interface System, BrainGate (http://www.braingate.org), for investigational clinical research use.

The first implantation of a system for recording single-unit activity was performed in 2004 and soon afterward, the first intracortically directed two-dimensional (2D) cursor movements and simple robotic control were accomplished by people with tetraplegia using an intracortical brain computer interface (iBCI; Hochberg et al., 2006; Kim et al., 2008). This early work also helped open the door to the first use of such arrays in epilepsy research (Waziri et al., 2009 and discussed below). Multidimensional (3D and above) control of a prosthetic or robotic arm including reaching and grasping followed within a few years (Hochberg et al., 2012; Collinger et al., 2013) and long-term recordings over years has now been possible (Simeral et al., 2011; Hochberg et al., 2012). Notably, these same intracortical electrode arrays simultaneously record single-unit action potentials and the full bandwidth of local field potentials (LFPs) and have permitted a deeper understanding of the collective neural dynamics in human neocortex (Truccolo et al., 2010). The ongoing research, in multiple laboratories, is heading toward improved decoding of neuronal ensemble activity (Malik et al., 2011; Wu et al., 2004; Yu et al., 2006; Wu and Hatsopoulos, 2006; Kim et al., 2008; Koyama et al., 2010; Paninski et al., 2010; Ajiboye et al., 2012; Jarosiewicz et al., 2013; Kao et al., 2014; Masse et al., 2014), creating improved communication systems for people with locked-in syndrome or ALS (Jarosiewicz et al., 2013; Bacher et al., 2014), control of prosthetic limbs or robotic assistive devices (as above), or reanimation of paralyzed limbs (Ethier et al., 2012; Moritz et al., 2008; Chadwick et al., 2011; Shanechi et al., 2014). Furthermore, there is increasing evidence that not only single-unit-level analysis but also information from multi-unit activity (MUA), local field potentials, and ongoing oscillatory activity, particularly in the high gamma band, may also carry important information for decoding movement related activity. In addition, though in this paper we focus on the clinical translation of single-unit and intracortical recordings, we note that other recording modalities, including scalp-based EEG and brain surface-based electrocorticography, are also being explored with similar goals (e.g., (Birbaumer et al., 1999; Hinterberger et al., 2003; Leuthardt et al., 2004; Sellers and Donchin, 2006; Miller et al., 2010; Vansteensel et al., 2010).

Ensembles of Single Neurons: Understanding and Treating Seizures

For the past 100 years, the study of brain activity in human epilepsy largely has been restricted to scalp-based EEG. Much like advances in the domain of motor prostheses, the predominant single-neuronal activity studies for understanding epilepsy have been performed in animal models. Unlike the motor prosthesis approach in which the similarity between nonhuman primate M1 and human M1 is evident in the underlying anatomy (and, as now being demonstrated, physiology), the relationship between any given animal model of epilepsy and the various forms of human epilepsy is unclear. Furthermore, few of the animal studies have actively investigated the role of action potential behavior in epileptiform activity. One notable exception included the use of action potentials for predicting and understanding the maturation of seizure activity (Bower and Buckmaster, 2008). In addition, a number of human studies have also gone beyond macroscopic scalp and intracranial EEG signals to examine neuronal spiking underlying seizures (Babb et al., 1973, 1981, 1987; Calvin et al., 1973; Halgren et al., 1977b; Wyler et al., 1982; Williamson et al., 1995). Wyler et al. focused on the relationship between single-neuron spiking and interictal discharges. In the same paper, they fortuitously captured seizure activity while recording from two single units and showed the expected increase in firing during spike-wave discharges both between seizures and during the seizure. Similarly, in a study focused on the amygdala and hippocampal formation, the few recorded neurons tended to increase their spiking rates during epileptiform activity (Babb et al., 1973) and were mostly related to auras and subclinical seizures.

Newer recording techniques focused on single units have further accelerated the pace of discovery for understanding

human epilepsy and the related roles of individual neurons. Work from Anton Bragin, Richard Staba, and colleagues have pioneered the importance of high-frequency oscillations (e.g., >100 Hz) in epilepsy (Bragin et al., 1999, 2002; Staba et al., 2002a, 2002b). Initial studies relied on microelectrodes to characterize these oscillations. They also explored the role of the single unit in these events and showed differences in single-unit activity in hippocampal regions of epileptic activity compared to the contralateral region. These studies helped pioneer a new concentration on the role and utility of high-frequency oscillatory activity in the localization of seizure onset areas and pathophysiology of seizures (Bragin et al., 2002; Staba et al., 2002a; Jacobs et al., 2008, 2010a, 2010b, 2012; Worrell et al., 2008; Zijlmans et al., 2009, 2011; Haegelen et al., 2013).

Along with the microwire approach, a laminar microelectrode probe was developed which can simultaneously acquire LFPs and multi-unit as well as single-unit activity (Ulbert et al., 2001). This probe allows for information to be gathered from multiple layers of the cortex in a single column simultaneously. This system has been used to explore the different laminar patterns of activation seen during interictal epileptiform discharges (Ulbert et al., 2004). The possible circuitry underlying locally generated events as opposed to propagated events was distinguished on the basis on involvement of deeper cortical layers—primarily layers IV and V.

An additional advance in understanding epilepsy has been the incorporation of the same microelectrode array platform that is being used in trials of BCIs in people with tetraplegia (Waziri et al., 2009). While this microelectrode array does not record from multiple layers in the same cortical column, it is optimized for recording many different single units. Several studies examining single-unit activity during either epileptiform activity (Keller et al., 2010) or the seizure itself (Truccolo et al., 2011, 2014) indicate that epileptiform events represent an interplay between multiple classes and types of neurons. This may be particularly true outside of the seizure focus—regions in which the epileptiform activity has propagated from a focus. In fact, the details of single-neuron activity in the "focus" itself remain poorly understood. It is possible that in the focus there is true hypersynchrony, which does not always fully propagate in each seizure to "outside" regions (Schevon et al., 2012; Jiruska et al., 2013). Nonetheless, the combined research using microelectrode and macroelectrode arrays has challenged the canonical framing of epilepsy as solely a disorder of hypersynchrony and imbalanced inhibition and excitation, which may be accurate at a superficial level but breaks down under more detailed mechanistic study. Furthermore, in some circumstances, a striking reproducibility of neuronal spiking patterns across different seizures has also been reported (Truccolo et al., 2011); the degree to which this is a universal feature is actively being investigated. Implications of this reproducibility extend to an understanding of the long-lasting impact of seizures on neuronal activity (Bower et al., 2015). The renewed recognition of the heterogeneous roles that single neurons may play before, during, and after a seizure implies a new wave of opportunity for diagnostic and therapeutic approaches in epilepsy and also serves to reinforce the clinical importance of ensembles of individual neurons which may be physically separated but critically linked by underlying collective dynamics. These opportunities for scientific discovery and therapeutic intervention are further enhanced by examining single-unit information in the context of mesoscale data that includes the LFP and MUA, and by consideration of basic neuronal biophysics and computation (Wei et al., 2014).

Preliminary findings at the single-unit level have suggested that there may be a neurophysiologic signature at the single-unit resolution that can be used to predict seizure onset. Predicting seizures has been the focus of many labs' work for a number of decades but the vast majority of prior efforts have focused on EEG or ECoG recordings. While these methods have recently moved toward devices and commercially supported clinical trials (Cook et al., 2013), none has led to a clinically useable or commercially successful predictive algorithm (Lehnertz et al., 2007; Mormann et al., 2007; Carney et al., 2011; Ramgopal et al., 2014). Truccolo et al. reported on changes in the single-unit activity that may occur a few minutes before the onset is detected on traditional ECoG (Truccolo et al., 2011). This finding partially recapitulates similar findings in animal models (Bower and Buckmaster, 2008). It is possible, therefore, that a renewed focus on the single neuron will overcome the barriers faced by the necessarily averaged multineuron recordings of EEG and ECoG. In an important related step, neural stimulation that is responsive to the detection of intracranially recorded epileptiform electrical activity recently has proven useful in reducing the frequency of clinically detected seizures (Morrell, 2011; Heck et al., 2014; Bergey et al., 2015).

Single Neurons in Movement Disorder Therapeutics

Compared to epilepsy, neuronal action potentials have been utilized far more often in understanding basal ganglia pathophysiology (DeLong et al., 1986; Penney and Young, 1986; Albin et al., 1989) and in treating movement disorders such as Parkinson's disease. Since early trials of placing deep brain-stimulating electrodes (DBS), single-unit recording has been a mainstay of both lesion procedures and electrode placements in helping to localize the electrode tip precisely within basal ganglia structures or subthalamic nuclei (Benabid et al., 1987; Bakay et al., 1992). For example, the boundaries of the subthalamic nucleus (STN) or globus pallidus internus can be determined based on firing rates and patterns that change as the electrode tip traverses a given region (Hutchison et al., 1998; Guridi et al., 2000; Benazzouz et al., 2002; Sterio et al., 2002). In fact, this may be the best example of using single-neuron activity in direct support of clinical activity. It has also been crucial in deepening our understanding of individual neuronal activity in the disease (reviewed in Bergman and Deuschl, 2002). This is particularly true with respect to movement disorders as the patients are usually conscious during surgery permitting direct tests of the relationship between recording, stimulation, neuronal activity, and resulting motor, sensory, and even affective consequences. Such investigations have led to insights into cognitive function (discussed below) and also on the fine-scale anatomy of basal ganglia structures such as the STN (Rodriguez-Oroz et al., 2001; Romanelli et al., 2004). Similar work has explored single-unit activity in the context of treatment of tremor and dystonia. Single-unit recordings from patients with tremor have led to an understanding of the role of individual basal ganglia and motor thalamic neurons that are capable of producing synchronized

rhythmic firing in a tremor related fashion (Lenz et al., 1988, 1993, 2002; Jeanmonod et al., 1996; Hua et al., 1998; Hurtado et al., 1999; Levy et al., 2000; Magnin et al., 2000; MacMillan et al., 2004). Furthermore, single-unit studies first in nonhuman primate models (Raz et al., 2001; Goldberg et al., 2002) and then later in clinical recordings have resulted in a model of basal ganglia function in which there is a pathological coupling in firing of basal ganglia neurons that, in turn, leads to synchronized firing of motor cortical neurons. This synchronization is hypothesized to relate to dopaminergic loss that, normally, maintains separation between basal ganglia subcircuits. When that dopaminergically maintained separation erodes circuit elements form larger, hypersynchronized networks (reviewed in Bergman and Deuschl, 2002; Engel et al., 2005). These microphysiological changes may be able to explain many elements of the disease and provide further targets for therapeutic intervention.

Single Neurons and the Mechanisms of Anesthesia

General anesthesia has, in many ways, been one of the key triumphs of medical and surgical practice. The safety profile of anesthetic agents, in conjunction with modern physiological monitoring tools, permits the tens of millions of safe surgeries that are performed worldwide each year. And yet, our understanding of the mechanisms of the agents used remains surprisingly rudimentary. In standard surgical practice, general anesthesia is induced with a fast-acting drug, such as propofol, causing unconsciousness within seconds. While the molecular actions of many of the anesthetics are well understood (e.g., propofol binds to GABA-A receptors and potentiates inhibitory inputs to the postsynaptic cell) their specific impact on overall neural circuits and neural activity remain unclear. The EEG under propofol general anesthesia is dominated by low-frequency, high-power slow oscillations (<1 Hz), increased gamma power, and an ~10 Hz alpha oscillation in frontal channels (Murphy et al., 2011; Cimenser et al., 2011; Purdon et al., 2013). The spike (action potential) activity underlying many of these patterns is not known, with the exception of slow oscillations during propofol induced anesthesia, described below. The slow oscillation was originally examined in animal studies, with some suggestion that it is globally synchronous across cortex. However, the small size of the brain in the animal models (e.g., rodents and cats) has prevented much analysis of large-scale relationships across the cortex, and human studies of scalp EEG provide little spatial resolution. Identification of the neural correlates of loss of consciousness is important both for clinical practice and in the scientific study of arousal and consciousness, as the neuronal patterns of activity can help elucidate the circuit dynamics underlying and ensuring the state of general anesthesia. To this end, several groups have begun exploiting single-unit recordings to understand the neurophysiological action of anesthetics. One set of recent studies has shown that propofol general anesthesia in humans causes slow oscillations and that these may be a mechanism by which propofol produces unconsciousness (Lewis et al., 2012, 2013). Single-unit recordings during loss of consciousness demonstrated that cortical neurons become phase locked to local slow oscillations but are out of phase with distant cortical areas, producing a fragmented network in which long-range cortical communication is disrupted. This "signature" of loss of consciousness suggests both a marker for anesthetic induced loss of consciousness and a possible mechanistic basis.

Single Neurons and Understanding Fundamental Cognitive Processes in Humans

In parallel with the direct utility of single-neuron exploration for diagnostic and therapeutic purposes has been a deep interest in examining the role of individual neurons in higher order cognitive processing. The combination of single-cell resolution and the ability to interact directly with a person during any number of behavioral tasks and scenarios has obvious power in trying to unlock the mysteries of human brain function (and dysfunction). Domains that have been explored cover a wide range of behavior and include memory, language and speech function, visual and auditory processing, motivation, reward and attention, as well as sleep and wakefulness (Patel et al., 2013). A complete exploration of these myriad topics is beyond the scope of this Perspective (but see Mukamel and Fried, 2012), but a few commonalities and emerging themes resulting from these studies are worth discussing. Perhaps most salient among these is that multiple studies now indicate that individual neurons in higher-order cortices maintain tuning properties or specificity for complex stimuli (Haglund et al., 1992; Fried et al., 1997; Chan et al., 2014). The most famous of these demonstrations, may be the discovery of a "Jennifer Aniston Neuron" by Fried and his group (Quiroga et al., 2005). This, and continued, elegant work has provided substantial evidence for neuronal selectivity and sparse encoding by neurons in various regions of the human brain (reviewed in Quiroga et al., 2008). Similarly exciting work has examined single-unit activity during memory processes. For example, hippocampal neuronal reactivation has been demonstrated during free recall (Gelbard-Sagiv et al., 2008) and spatial recall tasks (Miller et al., 2013). Equally provocative research has explored spatial navigation (Ekstrom et al., 2003), processing of language (Heit et al., 1988; Ojemann et al., 1988; Creutzfeldt et al., 1989; Engel et al., 2005; Tankus et al., 2012; Chan et al., 2014), decision, motivation, and volition (Fried et al., 2011; Patel et al., 2012; Sheth et al., 2012; Mian et al., 2014), and visual processing (Kreiman et al., 2000a, 2000b; Quiroga et al., 2005; Kreiman, 2007) including those of human faces by both patients with epilepsy (Heit et al., 1988) and patients with Autism Spectrum Disorder (Rutishauser et al., 2013).

Furthermore, these same recording techniques have been applied to an exploration of the underlying characteristics and mechanisms of sleep. In slow oscillations (Csercsa et al., 2010), the K-complex (Cash et al., 2009), and spindles (Nir et al., 2011), there has been an increasing understanding of the relationship between single-neuron activity and overlying local field potentials. While still in the early stages, these studies, which combine the microscale, single-cell resolution with mesoscale investigations, have provided a greater appreciation of the spatiotemporally complexity of sleep oscillations. Waves that are often portrayed as homogenous in their effects and spatial spread are, in fact, more heterogeneous in spatial representation and their involvement of individual neurons. This more nuanced view of sleep physiology dovetails well with the increasing appreciation of sleep as a period during which there

is likely to be memory consolidation as well as other forms of significant, higher cognitive processing (Stickgold et al., 2001; Walker and Stickgold, 2004; Diekelmann and Born, 2010).

While these findings are indeed not yet of immediate clinical relevance, they are crucial in gaining a deeper understanding of brain function. In addition, understanding the neural correlates of these various processes sets an essential foundation for the advanced treatment of cognitive deficits in both neurodegenerative and neuropsychiatric diseases.

Future Technologies Will Accelerate the Incorporation of Single-Neuron Activities into Clinical Practice

The previous discussions illustrate the ways in which the single unit is playing an increasing role in our understanding of normal function and disease (e.g., in epilepsy), in clinical application (for localization of nuclei in DBS placement), and even in developing direct therapeutic interventions (as in BCIs for restoring motor function). Although there is a more than 40-year history of considering cerebral action potentials in clinical thinking, single-unit physiology is still a small component of neurologic and psychiatric practice. It is likely, however, that changing technologies will accelerate the pace of utilization of micro- and mesoscale physiology in both research and clinical science.

One important technological step is the development of ever higher densities of electrode contacts to be used to acquire single-unit activity. Explorations in material sciences are also promising to make these arrays more reliable at the outset and over the long term. In addition, advances in fabrication approaches and electronics capabilities are yielding higher-density arrays of electrodes that can be deployed across wider areas of cortex. It is possible that even arrays that are not placed intracortically but that have high densities of microscale contacts and local active electronics (Viventi et al., 2011) will allow for recording of superficial unit activity even at the pial surface (Khodagholy et al., 2015). In addition, coupling single-cell resolution recordings directly with electrical stimulation or optical stimulation may provide new insights and opportunities (e.g., Wang et al., 2012).

As important as these direct technological developments are, there is also an increasing scientific effort required to process and understand the massive amount of data generated. Currently, patients and research participants whose cortical activity is recorded with a single (4 × 4 mm) Utah array can easily generate several Tb of data that contain information on 100+ neurons. Indeed, the full bandwidth of neural data when captured from one array at current resolutions produces ~500 GB per day. Continuous storage of neural data from one individual with two implanted arrays would yield 365 Tb in 1 year; this alone raises some interesting though not insurmountable issues. Beyond its simple storage, this much neural data challenges our computational capabilities and, essentially, our techniques for extracting meaningful information from this high dimensional dataset. Point process techniques, dimensionality reduction, data compression techniques, and other approaches are quickly evolving to assist single-unit neurophysiologists in making sense of these data.

Furthermore, as the technology for making single-unit recordings becomes more varied and commonplace, the environments in which it is being deployed increase as well. Single-unit recording systems are already present in in the operating room, epilepsy monitoring unit, and, in the rare clinical trial, in research participants' home settings. This relatively small group of patients/participants is likely to expand rapidly in the next few years to include patients in neurocritical care settings, patients with epilepsy in the outpatient settings, and patients with a wide variety of other neurological and neuropsychiatric diseases. The latter are especially likely as a result of the BRAIN initiative launched by President Obama in 2013 (Abbott, 2013; Church, 2013; Insel et al., 2013; Kandel et al., 2013; Samuel et al., 2013; The White House, 2013) and supported through NIH, NSF, and DARPA. There are already multiple projects funded which are focused on improving our ability to record from large numbers of single units not just in animal models but in clinical settings as well, and for possibly using these approaches for restoring memory function (e.g., the RAM project of DARPA) and neuropsychiatric balance (the SUBNETS project of DARPA). These ambitious undertakings are likely to accelerate the entry of single neuron physiology into clinical relevance in broad areas of neurology and psychiatry.

Conclusions

The study of single neurons, action potentials, and the activity of small ensembles of individual neurons have long been the gold standard for research and understanding in basic systems neurophysiology. Clinically indicated basal ganglia single-unit recordings are already a mainstay in DBS placement for movement disorders, and arrays of single-unit recordings are becoming more common in both subacute inpatient epilepsy monitoring and in neuroprosthesis research environments. These endeavors are only a first step in addressing the broader needs of people with the most common neurologic and psychiatric diseases. Whether focusing on traumatic brain injury, dementia, stroke, neuromuscular disease, major depression, bipolar disorder, schizophrenia, obsessive-compulsive disorder, or any number of other major illnesses, we need to bring the tools and insights of fundamental, single-unit neurophysiology to the clinical bedside. In doing so, there is great opportunity for basic science and clinical communities to learn from each other and to not only shed critical light on some of the most prevalent and difficult diseases affecting the brain but to create the next generation of neurotechnologies to maintain and restore neurologic function.

Indeed, the advent of clinically indicated, single-unit neurophysiology and associated technologies are changing how we frame questions in neurology and psychiatry. This shift to a more finely resolved and computationally enlightened approach to neurologic and psychiatric disease will begin to have a significant impact on the perspectives of the practicing clinician. Understanding the contribution of single units to the functional, physiologic basis of disease in a given patient and groups of patients will enable the neurorehabilitation or restoration of neural function. This shift is further amplified in combination with mesoscale information such as MUA or field potentials. When Kuffler and Nichols penned the classic text "From Neuron to Brain" (Kuffler and Nicholls, 1976), their stated aim was "to describe how nerve cells go about their business … how

these signals are put together, and how out of this integration higher functions emerge.'' Translational neuroscience and neuroengineering are on the threshold of incorporating this vital knowledge, one neuron at a time, into the care of people with neurologic or psychiatric disease.

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